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Published in:
New Biotechnology

DOI:
[10.1016/j.nbt.2016.09.003](https://doi.org/10.1016/j.nbt.2016.09.003)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Fugel, H-J., Nuijten, M., & Postma, M. (2016). Economic viability of Stratified Medicine concepts: An investor perspective on drivers and conditions that favour using Stratified Medicine approaches in a cost-contained healthcare environment. *New Biotechnology*, 33(6), 860-867.
<https://doi.org/10.1016/j.nbt.2016.09.003>

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Full length Article

Economic viability of Stratified Medicine concepts: An investor perspective on drivers and conditions that favour using Stratified Medicine approaches in a cost-contained healthcare environment

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ARTICLE INFO

Article history:

Received 25 May 2016

Received in revised form 7 September 2016

Accepted 21 September 2016

Available online 21 September 2016

Keywords:

Stratified medicine

Personalized medicine

Oncology

Reimbursement

Investments

Strategy

ABSTRACT

Rationale: Stratified Medicine (SM) is becoming a natural result of advances in biomedical science and a promising path for the innovation-based biopharmaceutical industry to create new investment opportunities. While the use of biomarkers to improve R&D efficiency and productivity is very much acknowledged by industry, much work remains to be done to understand the drivers and conditions that favour using a stratified approach to create economically viable products and to justify the investment in SM interventions as a stratification option.

Concept: In this paper we apply a decision analytical methodology to address the economic attractiveness of different SM development options in a cost-contained healthcare environment. For this purpose, a hypothetical business case in the oncology market has been developed considering four feasible development scenarios.

Conclusions: The article outlines the effects of development time and time to peak sales as key economic value drivers influencing profitability of SM interventions under specific conditions. If regulatory and reimbursement challenges can be solved, decreasing development time and enhancing early market penetration would most directly improve the economic attractiveness of SM interventions. Appropriate tailoring of highly differentiated patient subgroups is the prerequisite to leverage potential efficiency gains in the R&D process. Also, offering a better targeted and hence ultimately more cost-effective therapy at reimbursable prices will facilitate time to market access and allow increasing market share gains within the targeted populations.

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Introduction

As advances in science give the rise to increasingly precise tools for the diagnosis and treatment of disease, Stratified Medicine (SM) becomes a natural result of biomedical science and a promising path for the innovation-based biopharmaceutical industry to create new investment opportunities [1]. SM has the potential to improve medical outcomes for patients and economic outcomes for the healthcare system. Matching therapies to specific patient subpopulations using clinical biomarker/diagnostic-based SM offers the prospect of enhancing patient care with more effective and safe drugs, delivered with a greater probability of treatment success [2]. For industry, the SM approach provides an opportunity

to improve efficiency and productivity in the research and development (R&D) process and to demonstrate a differential therapeutic profile to be successful and rewarding in an increasingly competitive and cost-contained market environment. There have been several examples where SM has created clinical success and achieved accelerated product approvals, particularly in oncology (Glivec[®], Herceptin[®], Xalkori[®] and Zelboraf[®]) which have triggered increased investments in biomarker-based R&D by the industry in recent years [3]. However, the implementation and adoption of targeted therapies have been slower than many proponents have hoped or predicted, indicating possible concerns from investors about the economic viability of such approaches [4].

While the use of biomarkers to improve R&D efficiency and productivity is very much acknowledged by the industry, less is understood about the drivers and conditions that favour using a stratified approach to create economic viable products and to justify the investment in SM interventions as a stratification option. The commercial impact of using a diagnostic-guided

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strategy must be considered carefully in direct relation with patient access and benefits. Arguments over segmenting the market, and hence the loss of potential revenues, will be weighed against possible accelerated market and patient access with increasing market share gains within the target sub-population or faster market adoption [5]. Investigating and understanding of certain scenarios is critical for industry as several factors throughout drug development, reimbursement and market adoption affect the potential clinical and commercial success of a stratified medicine approach.

The differential therapeutic profile of SM could allow for more economic viable applications by addressing numerous offsetting factors which will influence investment decisions within the pharmaceutical and diagnostics industries. The objective of this paper is to explore these factors by developing a straightforward economic analysis for SM comparing different strategic options to help decision making for future R&D investments in an increasingly cost-contained healthcare environment. For this purpose, several case studies will be addressed.

Economic viability of stratified medicine

Pre-approval economic considerations

There is anticipation that SM not only provides better value for money, thanks to improving drug effectiveness and reducing toxicity, but could also help to reduce R&D costs. Notably, diagnostic testing may enhance the efficiency of clinical trials of new compounds and allow smaller and cheaper studies, still adequately statistically powered. This may occur if diagnostic testing information can identify a subgroup of patients most likely to respond to a given treatment and early enough reduce clinical trials sizes such that the drug development process can indeed become more efficient. Smaller and possibly shorter clinical trials are likely to reduce drug development costs and perhaps may allow earlier commercialisation of targeted therapies [6]. However, it is equally plausible that project specific investments in discovery and validation of biomarkers and diagnostic tests will involve additional costs and complexity to the inherently risky drug development process. Sometimes, the use of stratified clinical trial populations will involve comprehensive biomarker evaluation and validation steps, including an appropriate biomarker assay development in order to identify and test predictive biomarkers. Also, more narrowly defined inclusion criteria may lead to lengthier recruiting, the need for additional sites and higher costs.

Hence, since SM is in its early stages, it has been indicated that potential efficiency gains in R&D may only result in the long term [7]. In addition, from an economic perspective, a more targeted patient population may lead to smaller groups of eligible patients while R&D and other investment to bring products to market remain similar or even increase. In this case, premium prices seem inevitable and difficult discussions with reimbursement authorities emerge. Also, faster adoption or longer effective patent life for an SM intervention could be argued to offset the reduction in potential revenues from patient stratification. Yet SM may not only diminish groups of eligible patients, it can also enlarge them by redefining the disease space at the molecular level and across traditional disease boundaries (e.g. targeting solid tumours in oncology may be used for various cancer types) [8] or by extension of the target indication (move from 3rd line to 2nd or even 1st line) due to an increased cost-benefit ratio. All in all, if superior clinical performance is adequately evidenced, actual revenues might increase because SM enjoys faster and wider adoption [9].

In addition, diagnostic testing may improve a company's abilities to better identify promising drug candidates (assets) leading to higher probability of success of R&D projects due to

lower attrition rates in the R&D portfolio and lower sunk costs of failed R&D projects. In particular, it has been shown that reducing phase II and III attrition is the strongest lever for improving R&D efficiency and reducing the costs per New Molecular Entity (NME) [10]. However, a significant leverage of this impact on R&D budgets will require a certain number of targeted therapies with improved cost-benefit ratios as part of the company's development portfolio [11].

Time to product approval and commercialisation

The "time to market" is a key factor influencing the economic profile of a new compound and future cash-flows, which determine the economic value of a product. If an SM approach can shorten development time because diagnostic testing has streamlined the clinical trial programme, cash inflows will be shifted to earlier time periods, increasing the net present value of this compound. In addition, a compound reaching the market earlier can leverage longer periods of patent protections, which also increase expected economic returns [6]. Zelboraf[®] (vemurafenib) and Xalkori[®] (crizotinib) both achieved accelerated approvals (both approved by FDA in August 2011) and demonstrated that targeting can significantly shorten development time and cost [12,13]. Zelboraf[®] is used to target melanoma patients together with its companion diagnostic (BRAF gene mutation test) and reached the market within 4.5 years, including a regulatory approval time of 3.6 months, through an expedited process. Xalkori[®], was developed for the treatment of patients with non-small cell lung cancer (NSCLC) with a specific alteration in the ALK gene. The drug together with its ALK FISH probe companion diagnostic reached the market within 5 years from start of Phase I trials. Here, Pfizer used a stratified approach to establish clinical outcomes (i.e., safety and effectiveness) for the target populations involving only 255 patients. The approval process for the drug and its associated test took only 4.9 months, well ahead of standard review times for priority drugs [14].

Therapeutic effects and biomarker features

Prospective stratification is difficult and may also not always be feasible as scientific and clinical factors place some limits on the pace of development. In certain therapeutic areas, understanding of the molecular basis of diseases is insufficient to select biomarkers at early stage of development [15]. In addition, common disease conditions are often influenced by multiple genes/biomarkers in ways not always well understood in early development stages. In other therapeutic areas, there is no immediate medical need for diagnostic-based therapies. Gaining knowledge about the molecular mechanisms of diseases and the underlying common molecular pathways of how a drug interferes with next-generation genomic technologies is crucial for drug development before clinical symptoms and outcomes are studied in clinical trials [16]. Hence, predictive biomarkers can often be applied rather late in the clinical development programme, when clinical data show that an optimal benefit-risk profile is only achieved in a subpopulation of patients [8]. However, a decision of whether or not to continue clinical development, either with or without diagnostics, should ideally be made no later than at the end of Phase II [17] to allow for more efficient trial designs with smaller patient populations. Trusheim et al. [18] see three key factors when assessing therapeutic areas and biomarker features to drive economic value for stratified medicines compared to empirical medicines: the therapeutic effect with the selected population, the prevalence of the predictive biomarker and the clinical performance of the companion diagnostics (ability to distinguish treatment responders from non-responders).

Eventually, the value of investment in SM approaches is a function of both supply (scientific opportunities) and demand (market attractiveness) factors and will require systematic evaluation for each potential therapeutic area and its biomarker features. While oncology has been, up to now, at the forefront of SM approaches for many pharmaceutical and biopharmaceutical companies, other therapeutic areas such as immunology/transplant, CNS, infectious diseases and cardiovascular may hold great potentials over the next 10 years [19].

Given these challenges, many pharmaceutical and biopharmaceutical industries still use biomarkers as an add-on and not as an integral part of the strategy [5]. They employ biomarkers in the R&D process to keep an option for the full market potential rather than limiting themselves to a prospective stratification with a smaller population (“wait-and-watch” strategy). In fact, many stratified therapeutics on the market today were developed as the results of ‘rescue’ strategies to increase efficacy (KRAS/EGFR – Erbitux® and Vectibix® in oncology) or to avoid side effects (HLA-5701/Ziagen® in HIV) as a kind of salvage option. Consequently, from an investor perspective there is a clear need to understand the potential for stratification and to assess the value of having the option to stratify either prospectively or as fall back/project salvage option in case.

Downstream (post approval) economic considerations

The differential profile of an SM approach may positively affect commercial factors such as ‘time to market access’ and market uptake to increase products’ net present value. Several publications and economic analyses have assessed the economic potential of SM interventions, outlining key drivers shifting the sales and adoptions curve and enabling faster return on investment (ROI) [20,17,21]. It has become increasingly clear that early market penetration is important and can compensate for loss of market size. Higher and earlier market penetration, combined with attracting new patients and better compliance within a smaller market, can result in substantially different post-launch cash-flow profiles compared to empirical medicines and corresponding potential health gains for selected populations. However, the interdependency between drug and test will only enhance ROI where the related diagnostic testing has been effectively diffused into the market requiring appropriate commercialisation effort [22]. In addition, and adding to these complexities, gaining market share will be only feasible if reimbursement authorities likewise acknowledge the need for such diagnostics, for example as companion diagnostics of “expensive” biologicals in oncology, and if diagnostics are optimally aligned with patients’ needs.

Reimbursement and clinical adoption challenges

The uptake of SM in healthcare depends much on appropriate value assessment and the economic viability of such approaches in the healthcare setting. In an era of cost containment and limited health care resources, there is a clear need to consider the opportunity cost of decisions on which healthcare intervention to use, by demonstrating the potential added value of SM technologies, bring to the healthcare system. While pricing and reimbursement (P&R) of pharmaceuticals in many EU countries and the US can be characterised as somewhat “value-based”, the reimbursement of diagnostics is often resource or cost-based, with potentially relatively low reimbursement rates [23]. Especially in Europe, market access of higher priced molecular diagnostics tests is highly influenced by the existing reimbursement schemes. Moreover, in certain EU countries, market access for diagnostic-based therapies has been achieved only through subsidizations for the diagnostic test by pharmaceutical manufactures. Many

analysts have emphasised the need for more flexible pricing and reimbursement schemes to encourage innovation in SM and accelerate its adoption [24]. Generating robust clinical and health economic evidence may provide the confidence that enables payers to adopt potentially (cost-) effective tests more rapidly. Novel payment approaches and risk sharing agreements with third party payers are increasingly used to overcome the tension between funding new but expensive technologies and obtaining value for money where traditional reimbursement is not deemed appropriate. Such forms of market access schemes may be more appropriate to align the adequate incentives for various stakeholders involved in P&R decisions with long-term patient benefits, including associated funding schemes.

Driving diagnostic testing adoption is critical and associated with ensuring adequate test availability in clinical practice and by influencing healthcare provider competence in using these technologies. Efforts to educate physicians, other clinicians and patients on the use of new diagnostics is essential for a proper use of these technologies and may help to increase awareness and generate realistic expectations for SM interventions. There is also the need for an adequate health information infrastructure capable of accommodating and sharing complex medical information in a secure environment [25].

Strategic options for manufactures: framing the decision

Decisions to pursue an SM-approach versus conventional “treat-all” approaches are complex and depend on several factors, among them being patient population size, development cost (and patent status) and volume trade-offs, the potential for value differentiation and the payers (customers) ‘willingness to pay’ of the target population. Several examples of approved targeted therapies have demonstrated the clinical and economic value that SM can generate under specific conditions [18]. These examples also expose a diversity of development options outlining certain development and commercial challenges [26]. A company can follow:

- a) a **proactive approach**, where a biomarker-positive strategy is applied of enrolling only those patients in phase IIb/III clinical trials who were selected by the predictive biomarker/clinically useful diagnostic test and the drug is exclusively marketed for the targeted sub-population. Such an approach can shorten development time and costs if an improved targeted clinical profile meets qualifying criteria by FDA/EMA to leverage policy incentive tools such as fast track routes, accelerated approval or breakthrough therapy. It may also hold high potential for demonstrating value to third party payers and prescribing physicians. However, a key variable here involves ensuring that biomarker-driven work is initiated early enough to optimise a proactive approach by coordinating the timing of drug-diagnostic development in an effective way. Imatinib (Glivec®) is a specific example of a proactive SM development which has enhanced its clinical and commercial success. Despite a very small proportion of the patient population, Glivec® could leverage several offsetting factors such as shorter clinical trials, a premium price for the marketed drug, better compliance and high shares within the target population. Hence, Glivec® has been able to generate very high revenues (\$ 4.7 billion in 2014) and health gains given a high response rate among stratified patients and excellent curing capabilities for a serious disease like Chronic Myeloid Leukemia (CML). This example also shows that through the specific defining of the target populations, premium pricing could still go hand-in-hand with acceptable cost-effectiveness ratios [27]. Furthermore, the product was able to expand its initial indication to other diseases such as

Gastrointestinal Stromal Tumors (GIST). This principle of enlarging the patient population for targeted therapeutics has been demonstrated throughout the industry [28].

- b) a **reactive strategy** with late adoption of a stratified approach. Prospective stratification may not always be possible because of a lack of predictive biomarkers in early development stages. Rather in many cases potential biomarkers are one possible outcome of clinical trials that combine hypothetical stratifying biomarkers. There is also the case where safety and/or efficacy issues may arise during phase III clinical trials, which then drive the decision to adopt a patient stratification approach provided that a differential response in a pre-defined subgroup can be identified by a predictive biomarker/diagnostic test. While late adoption of SM approaches limits economic efficiency in drug development, it may provide a niche where economic value can be demonstrated for a company. However, an upward pricing option for post-approval stratification is limited because the reimbursement environment in many markets is inflexible with regard to price increases in such situations. Specific examples are panitumumab and cetuximab (in colorectal cancer) that revived once a target population (patients with EGFR-expressing metastatic colorectal carcinoma with a non-mutated wild-type KRAS genotype) was identified for which the drugs would be most valuable. Before the genetic marker was discovered, European regulators were reluctant to approve cetuximab (Erbix[®]) based on its questionable benefit risk profile [29].

Economic attractiveness of SM options

A decision-tree model (see Fig. 1) was constructed to assess the economic attractiveness of different development options based on various factors including development costs, the time of development and product approval, time-to peak sales (comprising time to market access & adoption rate), and peak sales prices, affecting the economic potential of an SM approach. The aim of this model is to explore the key value drivers and conditions affecting profitability of different SM scenarios. For this purpose, a hypothetical business case in the oncology market has been developed addressing 4 feasible scenarios. The discounted cash-flow model specifically investigated a new drug's Minimum Viable Market Share (MVMS) [30], i.e. the market share needed to break even in a risk-adjusted, expected net present value (eNPV) sense. Our analysis assumes a cost-effectiveness framework for the different development options in order to address third party payer considerations regarding reimbursement and affordability. While a cost-effectiveness analysis (CEA) allows payers' to have a formal method for determining value for a new technology, it also allows companies to determine their customer's maximum willingness to pay [31]. With this in mind, Table 1 shows the results from the 4 different scenarios (see Box 1 for a description of the methods and inputs).

According to Trusheim et al. the oncology market in US and EU can be segmented into multiple organ types [32], ranging from markets of approximately 500,000 new patients per year (i.e. 200,000 US and 300,000 EU-27) for the largest organ types (i.e. lung, breast, prostate and colorectal) to approximately 130,000 patients annually in second-tier organ types (e.g. pancreas, Non-Hodgkin's lymphoma) or to only 30,000–60,000 patients for most cancer organ -types, such as brain, multiple myeloma, Hodgkin lymphoma, etc [33,34].

S1 illustrates a business case for the development of empiric medicine for a large oncology such as breast or lung. The large cancer segment represents a highly competitive market environment with many therapeutics available. Hence, we assume that a new empiric treatment must at least achieve benchmark clinical

outcomes to ensure adequate market access and uptake and to justify certain price assumptions (US\$ 30,000), i.e. prove an acceptable cost-effectiveness to payers. S1 needs at least 6.9% of market shares at the time of peak sales in this segment to be break even (34,560 patient treated). This could be challenging as empiric therapies in this segment often start with a late stage positioning (stage III/IV); i.e. few patients to ensure patient access in an increasingly cost-conscious healthcare environment.

S2 illustrates an SM approach in large cancer (e.g. breast). The number of eligible patients is assumed to be 125,000, when targeting 25% of eligible patient population (as analogue to Herceptin[®]) via appropriate diagnostic. Improved clinical outcomes through stratification may allow an upward pricing (\$40,000) within a C/E framework. In this case, S2 needs at least 20.7% of market shares in this segment to be break even (with 25,875 patient treated). If we assume a 60% market share as in the Herceptin[®] example ("ideal situation" at that time) in this segment, eNPV would be at \$271 million; however more follow-up compounds have been developed in the meantime in this segment, which makes the market situation currently more challenging.

S3 illustrates an SM approach with a very low number targeted patient population (e.g. 5% as for Xalkori[®] in lung cancer), i.e. 25,000 patients, or addressing a rather small cancer segment (e.g. brain) via stratification. A differentiated therapeutic profile may capture disproportionate value through stratification while justifying a premium price (\$40,000) within a C/E framework. S3 needs at least 103% of market shares in this segment to be break-even (with 25,750 patient treated). This means S3 is never economically feasible under these conditions and will have to reduce development time and costs as well as to accelerate time to peak sales to become economically viable.

S4 illustrates a reactive SM business case in a large cancer (e.g. colorectal as analogue to Erbitux[®] and Vectibix[®]). Improved clinical outcomes may capture additional value within the target sub-population, however upward price flexibility is limited in this case. We have assumed a 65% targeted population similar to KRAS testing in colorectal cancer (i.e. 375,000 patients). S4 needs at least 10.6% of market shares in this segment to be break even (with 39,750 of patient treated).

Key economic drivers for SM options

The simulation scenario analysis for two proactive SM options (S2 and S3) outlined that changes of development time (e.g. from 8 to 5-years) and the time to peak sales (from 6 to 4-years) have the strongest impact on incremental eNPV's and MVMS for a company, while changes in development cost and transition probability will result in a lower impact on incremental cash flows (see Table 2).

The development of SM approach S3 for a very small sub-population (orphan-drug-model) will be economically viable when all economic drivers, including reduced development time and cost, together with an accelerated time to peak sales, are realised (52.2% MVMS or even 45% if we assume an increased transition probability in phase III from 0.69 to 0.80) [35]. This may be attainable in settings where there is no comparable alternative or currently available treatments are unsatisfactory. Xalkori[®], for example, needed 29 months in the US market to achieve 77% peak market share within the targeted population [36]. A slower market penetration with 8 years to reach peak will negatively influence the MVMS and Δ eNPV for both S2 and S3.

Discussion of key insights

Based on a straightforward model, our simulation analysis outlines the effects of development time and time to peak sales as

Fig. 1. Decision-tree model for SM treatment options.

Table 1

A economic model defining feasible development options in oncology.

Model parameter	Scenario S1 Empiric, large cancer (NSCLC, breast)	Scenario S2 stratified, large cancer (e.g. breast/Herceptin)	Scenario S3 Stratified, small cancer, organ types (brain etc) or large cancer with small population (e.g. Xalkori)	Scenario S4 Stratified, large cancer, re-active (e.g. Erbitux)
Cost of development (US\$ million)	500	500	500	550
Years of development & approval ('time to market')	8	8	8	9
Net patent life (years)	12	12	12	11
# of eligible patient/year (US + EU)	500,000	125,000	25,000	375,000
Price/revenue per patient Based on C/E ratio (Box 1)	30,000	40,000	40,000	30,000
Years to reach peak	6	6	6	6
Cost of revenue (%)	40	40	40	40
Market shares at peak of eligible patients where NPV is zero (MVMS in%)	6.9	20.7	103	10.6
Peak patient treated at MVMS	34,560	25,875	25,750	39,750
Discount rate (%)	10	10	10	10

Box 1. Methods and input sources.

- The decision tree analysis (DT) employs sequential decision making to see how the options to implement SM potentially demonstrate added value (eNPV). As such the DT incorporates dynamic decision-making considering new information throughout the development process. DT analysis incorporates average phase transition probabilities received from various sources [40] (i.e. phase I–II 0.70; phase II–III 0.39; phase III–approval 0.69) to risk-adjust the financial NPVs to expected NPVs (eNPV) for the scenarios.
- For all cases S1–S3 in Table 1, it is assumed that the development time (inclusive approval time) of an oncology drug requires 8 years and involves clinical out-of-pocket costs (direct costs) of US\$500 million. For S4, the re-active scenario, a 1-year longer time to market owing to the delay in the development of a companion diagnostic and additional costs of US\$ 50 million [15] for performing a retrospective biomarker/diagnostics validation after phase III are assumed. There are estimates of US\$1.2–1.8 billion as fully capitalized costs of the development of a new NCE comprising direct cash outlays of research and development [10], as well as the financing opportunity costs based on an 10% discount rate (cost of capital) [41]. The model explicitly incorporated this 10% cost of capital in its net present value (NPV) calculations for each scenario, thus, it is inappropriate to use the fully capitalized cost of US\$ 1.2–1.8 billion but rather only the out-of-pocket costs (direct cost).
- Stratified medicines, i.e. scenarios 2–4 also require the development of a companion diagnostic associated with additional costs and the cost per patients (including diagnostic assessments) will be higher on the one hand. While on the other hand, the number of patients for targeted treatments may be lower compared to empiric therapy, we assumed equal development cost for empiric versus SM options in the base case.
- Price/revenue per patient is related to favourable relative cost-effectiveness ratio (e.g. threshold of \$50,000 per QALY or Life saved) accepted by payers. Although we see market price levels of \$50,000–60,000 for certain large cancer segments and even higher prices for certain small cancer segments in some cases, we assumed prices of \$30,000 to 40,000 reflecting revenues per patient per year. These assumed prices should mirror increased therapeutic effects according to incremental cost-effectiveness ratio (ICER). Our price/revenue assumption took into consideration different treatment durations and potential discount/rebate requests certainly expected in some markets to achieve market access.
- The commercial time to reach peak sales is assumed to be the industry average of 6 years [42]. An analysis of financial reports of small, mid-size and large biopharmaceutical companies indicates an average cost of goods sold plus selling, general and administrative cost of 40% of sales.

Table 2

Simulated impact of key value drivers.

Model parameter	SM approach S2		SM approach S3	
	MVMS ^a in% at peak	Δ eNPV (US\$)	MVMS in% at peak	Δ eNPV (US\$)
5- years 'time to market'	17.1	\$46,51M	72.9	\$90,04M
5-years 'time to market' + 4-years to peak	14.1	\$46,53M	61	\$43,7M
+ \$100 M less development cost	12.1	\$31,5M	52.2	\$31,7M
+ increase to 0.80 transition probability in phase III	10.5	\$30,4M	45	\$29,8M
8-years to reach peak	25	–\$33,1M	112.5	–\$16,2M

^a MVMS = Minimum Viable Market Share where eNPV = 0; M = Million.

key economic value drivers. Substantial increases in eNPV occur when the proactive SM cases S2 and S3, as described in our hypothetical business case, can shorten the development programme and shift cash inflows to earlier time periods through faster commercialisation. Also, the acceleration of early market penetration has a substantial effect on future cash flows provided that the differential therapeutic profile will positively affect commercial factors, such as reimbursement and market uptake. However this case study in oncology showed that SM approaches for a very small sub-population (orphan-drug model) are only economically viable if several economic drivers, including reduced development time and costs, together with an accelerated market penetration, can be leveraged.

The results for this hypothetical business case are in line with previous economic studies in oncology confirming that substantial increases in eNPV occur when an SM approach will shorten development programmes and positively affects commercial factors such as market access and uptake [15,18]. While the 4 different development options (scenarios) considered here in oncology are non-exclusive, the principles of this economic assessment are also applicable to other therapeutic areas. However, the model parameter, as described in Tables 1 and 2 need to be adjusted accordingly for the economic modelling of new business cases.

There are several ways for the industry to achieve early commercialization, provided an improved targeted clinical profile meets qualifying criteria of FDA/EMA to leverage policy incentive tools such as fast track routes, accelerated approval or breakthrough therapy. Adaptive clinical trials in cooperation with regulatory bodies will play a pivotal role in this process to reduce time to market. There is also the need for an early and integrated collaboration between the pharmaceutical and diagnostic developers to maintain alignment across rapidly evolving and accelerated timelines for clinical trial and regulatory filings [37].

This analysis assumed a cost-effectiveness framework for the different development options in order to address payer-based considerations regarding reimbursement and affordability. This puts some limits on a premium pricing strategy in this hypothetical business case. However, the analysis showed that leveraging the identified key economic value drivers can make SM approaches potentially economically viable even with a rather “moderate” upward pricing assumption. Similar, Koelsch et al. in a recent publication argue for a new ‘balanced value’ business model for personalised medicine, reflecting a broader and faster market access with reimbursable prices for targeted therapies [11]. Globally, third party payers are increasingly conscious of the total budget impact of high-priced targeted therapies. As a number of new targeted therapies will enter the markets in the coming years, it is very likely that more restrictive caps on reimbursable prices for targeted therapies will be put in place in many healthcare systems. While Xalkori® and Zerboraf® were able to realise a substantial reduction of development time, their premium price strategies have induced market access delays (e.g. negative HTA recommendations from NICE) in many EU healthcare systems, resulting in reduced profitability. Identifying optimal prices for test-treatment combinations reflecting SM value propositions that can lead to ‘win-win’ scenarios for patients, individual payers and the healthcare system overall, will facilitate timely market access and uptake. This may also involve some value/profit sharing considerations between the pharmaceutical and diagnostic industries. Low reimbursement on a cost-based fee schedule and poor intellectual property may hamper diagnostic manufacturers to invest in ‘ideal’ studies to demonstrate clinical utility. Potentially, strategies should be developed to adequately provide the relevant incentives for innovations in this area.

Late adoption of an SM approach (S4) will limit economic efficiency in drug development, but may provide a niche wherein optimal value is demonstrated. The economic incentives are rather limited without earlier commercialisation opportunities, as well as without an upward pricing option, and may need to be weighed with potential additional market share gains based on improved therapeutic performance. In fact, reflecting the actual situation for Erbitux® in the EU in the years 2007–2009 showed an increase from 6671 patients treated for 16 weeks as 3rd line treatment in 2007 to 62,719 patients with KRAS wild-type as first-line treatment with 28 weeks treatment duration treated in 2009, driven by improved clinical benefits for the patients [38].

Conclusion and future perspective

This article has outlined key R&D related and commercially related value drivers which could explain the favourable economics for SM interventions under specific conditions. Decreasing development time and enhancing early market penetration would most directly improve the economic attractiveness of SM investments. In this analysis, we argue that factors such as reduced time to market due to accelerated approval or other expedited FDA/EMA programmes and earlier sales and faster uptake can substantially improve the economic viability of SM approaches in certain cases. However, the decision to pursue a proactive stratified approach depends much on the level of prior confidence in the predicted biomarker and a clear understanding about high value targets among pharmaceutical/diagnostics manufacturers and regulatory bodies. Offering a better targeted and hence ultimately more cost-effective therapy at reimbursable prices will facilitate time to market access and allow increasing market share gains within the targeted populations. Oncology and orphan diseases are areas where the science has advanced most and has triggered an increasing number of proactive stratified approaches, which are currently under development. Yet the development of an SM approach for a very small sub-population is unlikely to be economically feasible unless several economic drivers, including reduced development time and costs together with an accelerated market penetration, can be leveraged by a pharmaceutical company.

This analysis goes beyond standard NPV analysis to assess the economic attractiveness of SM approaches by incorporating decision tree (dynamic decision making) over traditional techniques. The analysis suggests performing early opportunity assessments to understand how the therapeutic effect of the treatment, characteristics of the identified patient population and test performance interact and affect the commercial value of stratification. This should support a company’s ability to generate a highly differential therapeutic profile for a subgroup of patients, enhancing the value proposition of SM interventions for third party payers and prescribing physicians [15]. Understanding of certain scenarios is critical and should help manufacturers to prioritise investment decisions, including whether or not to generate more evidence. Effective partnering approaches are needed to share risk and reward to realise efficiency gains in the R&D process and to ensure incentives for biomarker/diagnostic companies. This may evolve new business models with a further focus on co-operation between different industry sectors, and with academia including public-private partnerships.

The conceptual attractiveness of targeting may also reduce development costs if failure rates of R&D projects and associated sunk costs can be avoided, especially of late phase clinical trials. Hence, in the long-term, a higher percentage of SM projects into R&D portfolio may enhance overall R&D productivity as more promising drug candidates (assets) with better benefit-risk profiles will reduce risk and cost of attrition. This should improve a company’s

future ROI and may further stimulate private sector investments in SM interventions. The recent benchmark report by the Diaceutics group ‘Pharma Readiness for Personalized Medicine 2016’ estimated that almost 75% of assets currently in late stage development could potentially benefit from a targeted approach [39].

Industry alone will be unable to successfully leverage the key economic drivers for SM interventions outlined in this research. New regulatory approaches including adaptive clinical trial design must be forward looking and prepared for the introduction of new biomarker/diagnostic technologies to support their timely access to targeted medicines. In addition, creative reimbursement models, using managed entry agreements and value-based pricing for drugs and diagnostics should provide incentives for appropriate evidence generation and alignment between various stakeholders to ensure patient access to SM interventions. Another factor influencing development and diffusion of SM interventions relates to an adequate information technology infrastructure capable of storing and sharing complex medical information in a secure environment [25]. Developing standards in electronic medical record and tissue storage (for example biobanking), as well as dealing with the privacy and ethical issues in DNA collection, are key challenges to be addressed by various stakeholders and health policy.

Adopting SM approaches into clinical practice continues to provide challenges for manufacturers, regulators, payers and providers which must be addressed in a collaborative and synergistic way to enhance patient outcomes. Because the economic challenges and opportunities of SM are intimately linked by many factors, both internal and external to the development and clinical adoption process, unprecedented alignment of incentives will be required among all stakeholders to realise the full potential of SM interventions.

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